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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,190	GRIMPE ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,10-17,21-28,35 and 37-54* is/are pending in the application.

4a) Of the above claim(s) *4,7,10,11,14-16,21,22,27,35 and 37-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,13,17,23-26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 25 November 2009.

Claim Status

Claims 1, 4, 7, 10-17, 21-28, 35 and 37-54 are pending. Claim 28 is amended. Claims 2-3, 5-6, 8-9, 18-20, 29-34, 36, 55-56 are cancelled. Claims 4, 7, 10-11, 14-16, 21-22, 27, 35, 37-54 were withdrawn by the examiner in the previous Office Action, as being drawn to non-elected inventions. Claims 1, 12-13, 17, 23-26 and 28 are under current examination.

Priority

This application claims benefit from provisional U.S. Application No. 60/423,082 filed 1 November 2002 and claims benefit from provisional U.S. Application No. 60/471,447 filed 16 May 2003. The instant application has been granted the benefit date, 1 November 2002 from the application 60/423,082.

RESPONSE TO ARGUMENTS

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 12-13, 17, and 23-26 remain rejected under 35 U.S.C. 103(a) as being obvious over unpatentable over Fawcett et al. (Brain Research Bulletin. 1999; 49(6):

377-391) in view of Kleesiek (WO01/49831) and further in view of Jen et al. (Stem Cells 2000; 18:307-319) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant makes the specific arguments:

(1) Fawcett et al. in view of Kleesiek and Jen et al. do not teach or suggest to the skilled artisan that inhibiting expression of activity of XT-I and XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi can and/or will reduce glycosaminoglycan content in a glial scar of a mammal. The examiner has made a prima facie case of obviousness for the claimed invention. This has been addressed several times during prosecution (See Action, filed 5/27/2009 and pending rejection). Therefore, the examiner concludes the applicant's argument is that the cited art is not enabling. The Office has a policy of viewing the art of antisense inhibition of gene expression as being enabled, if the sequence of a specific gene is known. The examiner had consulted with an examiner in the art unit that examines most antisense, RNAi, and siRNA applications regarding the enablement of this invention while preparing one of the earlier rejections of the instant claims. Therefore, the examiner presumes all art used in the pending rejection is also enabled. Accordingly, the examiner finds this argument unpersuasive. Elsewhere in his remarks, the applicant has argued against the cited art providing an enabling disclosure of the suggested invention (Remarks, page 16, line 15+). As indicted above the Office views nucleic acid inhibition of known genes to be enabled and predictable.

The applicant indicates (Remarks, page 18, parag.2-3) that the state of the art is unpredictable in regards to *in vivo* antisense treatments. Among the references cited by the applicant to support this assertion, *Mahato* indicates that "one FDA-approved antisense drug is in the clinic," thereby indicating a measure of success. Additionally, another reference cited by the applicant to demonstrate unpredictability and lack of enablement, particularly *Wood et al.,* state "progress in the field of RNA therapeutics over the last decade has been remarkable. A large number of antisense oligonucleotide agents are in clinical development, including those...[in] Phase I and II clinical trials...Therapeutic RNAi developments are not far behind." Therefore, the examiner concludes there is sufficient reason to conclude the technology is enabled and predictable. Accordingly, the examiner finds the applicant's arguments unpersuasive.

(2) The Office provides no teaching or suggestion of administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar. The examiner suggests that in light of the recent KSR decision, this necessity for a "reason or suggestion" is no longer required. KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision Ex parte Smith, -- USPQ2d, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Furthermore, the examiner has provided some of the following in previous actions and the pending rejection: Fawcett suggest inhibiting GAG formation to prevent gliosis. Kleesiek teach the nucleic acid sequences of XT-I and XT-II and further suggest methods of gene therapy and methods of inhibiting XT-I and XT-II.

Additionally, Kleesiek teach that XT-I and XT-II are involved in the synthesis of GAG. A skilled artisan knowing that inhibiting XT-I and/or XT-II expression is capable of inhibiting the synthesis of GAG would seek methods of inhibiting XT-I and/or XT-II; agents used in gene therapy methods such as DNAzymes would be among those considered by a skilled artisan. Jen et al. is a review article about designing antisense oligonucleotides, ribozymes, and DNAzymes in which Jen et al. teaches "the DNAzyme can be made to cleave virtually any RNA that contains a purine-pyrimidine junction" (page 312, col.2). A skilled artisan having the knowledge of Jen and Kleesiek and Fawcett would be able to make a DNAzyme to inhibit XT-I and/or XT-II, with the knowledge that these molecules would be agents that could inhibit GAG formation in glial scars. Accordingly, the examiner concludes that a skilled artisan would find that the cited art suggests inhibiting expression or activity of XT-I or XT-II using nucleic acid agents (RNAi, DNAzymes, Ribozymes, antisense) can and/or will reduce glycosaminoglycan content in a glial scar of a mammal. There is a scientific rationale for using intrathecal, topical or local administration of agents to the glial scar. The Jen article discusses the issues required for RNAi, DNAzymes, Ribozymes, and antisense drugs to provide therapeutic effects, including drug delivery and localization. A skilled artisan, knowing the difficulties in delivering drugs to neurons and the requirement that the nucleic acid drugs listed above would require co-localization within the same intracellular compartments as the mRNA being targeted, would choose routes of administration such as intrathecal, topical or local administration. Therefore, a skilled artisan would be deem it scientifically logical to use intrathecal, topical or local

administration to deliver RNAi, DNAzymes, Ribozymes, and antisense drugs. These issues have been addressed in previous actions (e.g., Action, filed 5/27/2009, pages 4-6). Accordingly, the examiner finds the applicant's argument unpersuasive.

The applicant has further argued (page 19, section "b") that the rejection provides no reasonable rationale that the cited references teach or suggest administering the antisense oligonucleotides, ribozymes, or RNAi agent intrathecally, topically, or locally to the glial scar. This has been addressed previously. The applicant indicates that he believes there is no discussion of the scientific rationale for using RNAi, DNAzymes, Ribozymes, and antisense drugs. In particular, the applicant suggests that a reference, such as Jen et al, which discusses RNAi, DNAzymes, Ribozymes, and antisense drugs would not guide a skilled artisan to use them. This is spurious argument. Of course a skilled artisan would be guided by the Jen reference to use RNAi, DNAzymes, Ribozymes, and antisense drugs. Jen et al. is a review article which describes making and using a variety of RNAi, DNAzymes, Ribozymes, and antisense oligonucleotides for inhibiting gene expression. The examiner has provided a *prima facie* argument of obviousnesss, but is not required to supply a dissertation regarding the use of RNAi, DNAzymes, Ribozymes, and antisense drugs. According to the law, this is sufficient. Therefore, the examiner finds the applicant's argument unpersuasive.

More simply, the scientific logic for practicing the instant invention is this: (1) The cited art (Fawcett) teaches that damaged axons in the CNS do not regenerate because of the inhibitory nature of glial scars and that preventing GAG chain synthesis suppresses scar formation, (2) Fawcett suggests targeting GAG synthesis and provides

a variety of methods, but does not recite using antisense nucleic acids, (3) Kleesiek discovered the genes for xylosyltransferase-I (XT-I) and xylosyltransferase-II (XT-II) which are required for GAG biosynthesis and further teach generic inhibitors of XT-I and XT-II, and (4) Jan et al. teach that any known gene can be inhibited using RNAi, DNAzymes, Ribozymes, and antisense drugs; therefore, a skilled artisan would deem it scientifically logical to use RNAi, DNAzymes, Ribozymes, and antisense drugs targeted against XT-I or XT-II to inhibit GAG chain biosynthesis to suppress glial scar formation.

(3) Fawcett et al. teach away from inhibiting expression or activity of XT-I and XT-II as a means to reduce glycosaminoglycan content in a glial scar of a mammal. In particular, the applicant points out that Fawcett et al. suggest targeting TGF-β with antibodies rather than using antisense oligonucleotides, ribozymes, DNA enzymes or RNAi to inhibit expression of XT-I or XT-II. Fawcett makes clear that preventing synthesis of proteoglycans is a potential method of reducing glial scars and promoting axonal regeneration. Fawcett offers only a couple of ideas for preventing synthesis of proteoglycans which include (1) blocking cytokines produced by glial scars and (2) treatment with chlorate and xylosides. While Fawcett et al. point a skilled artisan in the direction of preventing synthesis of proteoglycans as a method for reducing glial scars and promoting neuronal regeneration, Fawcett does not suggest the method of inhibiting glial scarring caused by proteoglycan synthesis with administration of RNAi, DNAzymes, Ribozymes, and antisense drugs. However, there is nothing in Fawcett that indicates that inhibiting glial scarring caused by proteoglycan synthesis by administering some agent would not be successful. Rather, the teachings of Fawcett

would encourage a skilled artisan to look for alternative (i.e., non-toxic) approaches to inhibiting glial scarring caused by proteoglycan synthesis. Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant further argues that Fawcett teaches away from inhibiting expression or activity of XT-I and XT-II as a means to reduce glycosaminoglycan content in a glial scar of a mammal (Remarks, page 21+, section "c"). The applicant points to a specific passage of Fawcett at page 384, col.2, parag.2 which suggests preventing synthesis of chondroitin sulfate GAGs. However, Fawcett teaches a variety of methods for reducing glycosaminoglycan content in glial scars, including "preventing GAG chain sulphation, GAG chain synthesis, or by treatment with chondroitinase" (page 383, col.2, lines 2-5). In addition, Fawcett teaches that there are at least 4 different means to promote axon regeneration: (a) remove cells that produce molecules that inhibit axon regeneration, (b) reduce synthesis of molecules that inhibit axon regeneration, (c) block the activity of molecules that inhibit axon regeneration, and (d) degrade molecules that inhibit axon regeneration (page 384, col.1, last parag.). Furthermore, Fawcett teaches that chondroitin sulphate proteoglycans are molecules which inhibit axon/neurite growth. Taken as a whole, the review article, Fawcett, provides many options for treating glial scars and a skilled artisan would not be limited by the single passage cited by the applicant when devising methods of reducing glycosaminoglycan content in a glial scar of a mammal. Accordingly, the teachings of the cited art do not "teach away" from the claimed invention and examiner finds the applicant's argument unpersuasive.

(4) The most recent Office Action has provided no evidence in fact or technical reasoning that it was known at the time of the invention that the glycosaminoglycan content of a glial scar of a mammal is directly or indirectly related to the expression of activity or XT-I or XT-II in a subject. The examiner acknowledges that no single piece of cited art explicitly demonstrates a link between Xylotransferase-I (and/or Xylotransferase-II) and the glycosaminoglycan content of a glial scar. However, Kleesiek teach that XT-I and XT-II are enzymes required for the biosynthesis of glycosaminoglycan (page 2, line 8) and Fawcett teach that (1) glial scars produce GAG and (2) high concentration of proteoglycans inhibit growth of axons (page 382, col.1). Additionally, Fawcett suggest the general "strategy..to target proteoglycan synthesis…[in order] to find a means of preventing the synthesis specifically chondroitin sulphate GAGs" (page 384, col.2, *Preventing Synthesis* section). Therefore, the examiner has attempted to show that a skilled artisan, having read the cited art, would understand this connection. The examiner has presented a *prima facie* case that the cited art suggests that inhibiting expression or activity of XT-I or XT-II using nucleic acid agents (RNAi, DNAzymes, Ribozymes, antisense) can and/or will reduce glycosaminoglycan content in a glial scar of a mammal. It is through the establishment of a reasoned basis for a suggestion of this method, that the examiner finds the cited art suggests that the glycosaminoglycan content of a glial scar of a mammal is directly or indirectly related to the expression of activity or XT-I or XT-II in a subject.

The cited art suggests a strategy for inhibiting expression or activity of XT-I or XT-II using nucleic acid agents (RNAi, DNAzymes, Ribozymes, antisense) that can

and/or will reduce glycosaminoglycan content in a glial scar of a mammal. Fawcett suggests preventing synthesis of glycosaminoglycan (GAG) in a glial scar can promote neural regeneration (page 384, *How Might Axon Regeneration Be Promoted?* and *Preventing Synthesis of Inhibitory Molecules* sections). Kleesiek teaches XT is an enzyme in the biosynthesis of the glycosaminoglycan. A skilled artisan, knowing that preventing synthesis of glycosaminoglycan in a glial scar can promote neural regeneration, would seek methods to inhibit glycosaminoglycan. A skilled artisan might ask himself how he could inhibit GAG expression. A skilled artisan in seeking such information would come upon Kleesiek. Kleesiek teach the nucleic acid sequences of XT-I and XT-II and further suggest methods of gene therapy and methods of inhibiting XT-I and XT-II. A skilled artisan knowing that inhibiting XT-I and/or XT-II is capable of inhibiting the synthesis of GAG would seek methods of inhibiting XT-I and/or XT-II; agents used in gene therapy methods such as DNAzymes would be among those considered by a skilled artisan. Jen et al. is a review article about designing antisense oligonucleotides, ribozymes, and DNAzymes in which Jen et al. teach "the DNAzyme can be made to cleave virtually any RNA that contains a purine-pyrimidine junction" (page 312, col.2). A skilled artisan having the knowledge of Jen and Kleesiek and Fawcett would be able to make a DNAzyme to inhibit XT-I and/or XT-II, with the knowledge that these molecules would be agents that could inhibit GAG formation in glial scars. Accordingly, the examiner concludes that a skilled artisan would find that the cited art suggests inhibiting expression or activity of XT-I or XT-II using nucleic acid agents (RNAi, DNAzymes, Ribozymes, antisense) can and/or will reduce

glycosaminoglycan content in a glial scar of a mammal. Therefore, a skilled artisan would understand that the glycosaminoglycan content of a glial scar of a mammal is directly or indirectly related to the expression of activity or XT-I or XT-II in a subject. Accordingly, the examiner finds this particular argument unpersuasive.

The applicant further argues Kleesiek et al. do not teach that a glycosaminoglycan reducing effect results from a lack of XT activity or expression. While Kleesiek does not provide a teaching exactly as the applicant has expressed it, Kleesiek does teach that "alterations in XT activity have been reported to be associated with fibrotic and sclerotic alterations of connective tissue" (page 9, lines 10-14). In this citation, Kleesiek refers to the work of Gotting, who teaches that XT activity is a confirmed biochemical marker for the determination of fibrotic activity. Therefore, a skilled artisan being aware that glycosaminoglycans are associated with fibrosis and tissue scarring would now be apprised of the link between XT activity and tissue scarring. As Fawcett suggests preventing synthesis of glycosaminoglycan (GAG) in a glial scar can promote neural regeneration, a skilled artisan would understand that the glycosaminoglycan content of a glial scar of a mammal is directly or indirectly related to the expression of activity or XT-I or XT-II in a subject and that a glycosaminoglycan reducing effect results from a lack of XT activity or expression. Accordingly, the examiner finds the applicant's argument unpersuasive.

(5) The applicant argues that the specification shows objective evidence of nonobviousness (Remarks, page 23). After detailing the successes of inhibiting glial scar formation using nucleic acids targeted against XT-I (as described in Specification,

Example 8) and the post-filing, *Brain* 2008 article, the applicant states "[t]hese results are unexpected in view of the teachings of the prior art which fail to show any evidence that inhibiting expression of XT-I can be used to promote neuronal regeneration." The cited art has demonstrated that inhibition of GAG formation promotes neuronal regeneration. Targeting expression of XT-I as a means to promote neuronal regeneration is not demonstrated by the cited art. However, using nucleic acids (e.g., RNAi, DNAzymes, Ribozymes, antisense) to inhibit XT-I or XT-II expression is deemed by the Office to be enabled and suggested by the cited art (Kleesiek and Jan). Accordingly, the Office views the claimed method as obvious. Demonstrating this effect *in vivo* is not deemed to be nonobvious.

(6) The applicant also argues that claims 25 and 26 are patentable over the cited art because they fail to explicitly teach the co-administration of neurotrophic factors. Fawcett suggests using trophic factors for promoting axonal regeneration (page 381, col.2, lines2-4). Additionally, the Conclusion of Fawcett suggests controlling recruitment of different cell types using trophic factors. Furthermore, Fawcett contains the phrase, "exposure to neurotrophins blocks inhibition of axonal regeneration" (page 387, col.1). In the context of Fawcett, a skilled artisan would view treatment of glial scars with "trophic factors" as suggesting neurotrophic factors. While Fawcett indicates that several different growth factors can be used to help regenerate neurons, none of the cited art specifically recites using nerve growth factor (NGF). However, as the scope of the method is involved in regenerating neurons, the examiner asserts a skilled artisan would use neurotrophic factors, such as nerve growth factor in a method of

inhibiting glial scars and promoting neuronal regeneration because NGF induces the differentiation and survival of neurons and is critical for the survival and maintenance of sympathetic and sensory neurons. Therefore, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1, 12-13, 17, and 23-26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fawcett et al. in view of Kleesiek and further in view of Jen et al.

The examiner reiterates the pending rejection:

Claims 1, 12-13, 17, and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fawcett et al. (Brain Research Bulletin. 1999; 49(6): 377-391) in view of Kleesiek (WO01/49831) and further in view of Jen et al. (Stem Cells 2000; 18:307-319).

Claim 1 is directed to a method of reducing glycosaminoglycan (GAG) content in a glial scar of a mammal comprising administering to the glial scar of the mammal an agent that inhibits the expression and/or activity of a chain initiation enzyme wherein the agent is selected from the group consisting of antisense oligonucleotides, ribozymes, DNA enzymes, and RNAi constructs, the agent targeting a nucleic acid sequence encoding xylotransferase I (XT-I) or xylotransferase II (XT-II); wherein the agent is administered intrathecally, topically, or locally to the glial scar.

Claim 17 is directed to a method of promoting neuronal regeneration in a subject comprising administering an agent to the to a nervous system lesion to inhibit a GAG chain initiation enzyme, wherein the agent is selected from the group consisting of

antisense oligonucleotides, ribozymes, DNA enzymes, and RNAi constructs, the agent targeting a nucleic acid sequence encoding xylotransferase I (XT-I) or xylotransferase II (XT-II); wherein the agent is administered intrathecally, topically, or locally to the nervous system lesion; wherein the neuronal regeneration includes neurite extension into the nervous system lesion.

The remaining claims are directed to the agent being a DNA enzyme (claims 12 and 23) and wherein there is an additional administration of a growth factor or neurotrophic factor (claim 25). Claims 13 and 24 are directed to specific DNA enzymes SEQ ID NO:33 and 39.

Fawcett et al. teach damage to the CNS results in formation of glial scars (abstract) and chondroitin sufphate glycosaminoglycan (GAG) expression is increased around the glial scars of CNS injury (page 382, col.1, lines 1-10) and that GAG expression around glial scars inhibit axon growth (page 382, col.2, lines 8-15). Fawcett et al. teach "disruption of proteoglycan synthesis...has been shown to reduce inhibition [of glial growth]" (page 382, col.2, lines 10-11). Fawcett et al. teach "How might axon regeneration be promoted?...If one wishes to reduce the influence of inhibitory molecules how might one do it? Essentially the options are to remove the cells that produce them, to reduce their synthesis, to block their activity, or to degrade them." (page 284, col.1).

Fawcett et al. do not specifically suggest using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II.

Kleesiek teaches cloning of cDNA of human and rat xylotransferase-I and xylotransferase-II (XT-I and XT-II) and expression of recombinant proteins (abstract). Kleesiek teaches XT is the initial step enzyme in the biosynthesis of the glycosaminoglycan linkage region. (page 2, lines 8-9). Kleesiek teaches "knowledge of the cDNA sequence of XT allows to use it on gene level such as in gene diagnostic or gene therapy" (page 2, lines 25-26). Kleesiek suggests making medicaments which are inhibitors of xylosyltransferase (page 17, lines 3-4).

Kleesiek does not specifically teach using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II.

Jen et al. is a review article about designing antisense oligonucleotides, ribozymes, and DNAzymes. Jen et al. teaches "the DNAzyme can be made to cleave virtually any RNA that contains a purine-pyrimidine junction" (page 312, col.2). The examiner believes that these teachings along with the teachings of Kleesiek which describe the DNA sequence for xylotransferase-I and xylotransferase-II, make any DNA enzyme obvious.

Claim 26 is directed to the method of claim 25 and further requiring administration of nerve growth factor. Fawcett suggests using trophic factors for promoting axonal regeneration (page 381, col.2, lines2-4). Additionally, the Conclusion of Fawcett suggests controlling recruitment of different cell types using trophic factors. Furthermore, Fawcett contains the phrase, "exposure to neurotrophins blocks inhibition of axonal regeneration" (page 387, col.1). In the context of Fawcett, a skilled artisan would view treatment of glial scars with "trophic factors" as suggesting

neurotrophic trophic factors. While Fawcett indicates that several different growth factors can be used to help regenerate neurons, none of the cited art specifically recites using nerve growth factor (NGF). However, as the scope of the method is involved in regenerating neurons, the examiner asserts a skilled artisan would use neurotrophic factors, such as nerve growth factor in a method of inhibiting glial scars and promoting neuronal regeneration because NGF induces the differentiation and survival of neurons and is critical for the survival and maintenance of sympathetic and sensory neurons.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to reduce GAG content in a glial scar and promote neuronal regeneration in a subject by inhibiting XT-I or XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs.

The person of ordinary skill in the art would have been motivated to combine the teachings of Fawcett et al., Kleesiek, and Jen et al. in a method using DNA enzymes (and other inhibitors of mRNA) to XT-I or XT-II to inhibit glial scar formation and promote neural regeneration. Fawcett et al. suggest that inhibiting synthesis of GAG would promote neuronal regeneration, while Kleesiek et al. suggest inhibiting XT using knowledge of the XT cDNA sequence and Jen et al. suggest ribozyme, DNAzyme and antisense design for any DNA sequence.

The cited art suggests the methods of the instant claims. Fawcett suggests preventing synthesis of glycosaminoglycan (GAG) in a glial scar can promote neural regeneration (page 384, *How Might Axon Regeneration Be Promoted?* and *Preventing Synthesis of Inhibitory Molecules* sections). Kleesiek teaches XT is an enzyme in the

biosynthesis of the glycosaminoglycan. A skilled artisan, knowing that preventing synthesis of glycosaminoglycan in a glial scar can promote neural regeneration, would seek methods to inhibit glycosaminoglycan. As skilled artisan might ask himself how he could inhibit GAG expression. A skilled artisan in seeking such information would come upon Kleesiek. Kleesiek teach the nucleic acid sequences of XT-I and XT-II and further suggest methods of gene therapy and methods of inhibiting XT-I and XT-II. A skilled artisan knowing that inhibiting XT-I and/or XT-II is capable of inhibiting the synthesis of GAG would seek methods of inhibiting XT-I and/or XT-II; agents used in gene therapy methods such as DNAzymes would be among those considered by a skilled artisan. Jen et al. is a review article about designing antisense oligonucleotides, ribozymes, and DNAzymes in which Jen et al. teaches "the DNAzyme can be made to cleave virtually any RNA that contains a purine-pyrimidine junction" (page 312, col.2). A skilled artisan having the knowledge of Jen and Kleesiek and Fawcett would be able to make a DNAzyme to inhibit XT-I and/or XT-II, with the knowledge that these molecules would be agents that could inhibit GAG formation in glial scars. Accordingly, the examiner concludes that a skilled artisan would find that the cited art suggests inhibiting expression or activity of XT-I or XT-II using nucleic acid agents (RNAi, DNAzymes, Ribozymes, antisense) can and/or will reduce glycosaminoglycan content in a glial scar of a mammal.

There is a scientific rationale for using intrathecal, topical or local administration of agents to the glial scar. The Jen article discusses the issues required for RNAi, DNAzymes, Ribozymes, and antisense drugs to provide therapeutic effects, including

drug delivery and localization. A skilled artisan, knowing the difficulties in delivering drugs to neurons and the requirement that the nucleic acid drugs listed above would require co-localization within the same intracellular compartments as the mRNA being targeted, would choose routes of administration such as intrathecal, topical or local administration. Therefore, a skilled artisan, having read Jen et al., would be deem it scientifically logical to use intrathecal, topical or local administration to deliver RNAi, DNAzymes, Ribozymes, and antisense drugs.

More simply, the scientific logic for practicing the instant invention is this: (1) The cited art (Fawcett) teaches that damaged axons of the CNS do not regenerate because of the inhibitory nature of glial scars and that preventing GAG chain synthesis suppresses scar formation, (2) Fawcett suggests targeting GAG synthesis and provides a variety of methods, but does not recite using antisense nucleic acids (3) Kleesiek discovered the genes for xylosyltransferase-I (XT-I) and xylosyltransferase-II (XT-II) which are required for GAG biosynthesis and further teach generic inhibitors of XT-I and XT-II, and (4) Jan et al. teach that any known gene can be inhibited using RNAi, DNAzymes, Ribozymes, and antisense drugs; therefore, a skilled artisan would deem it scientifically logical to use RNAi, DNAzymes, Ribozymes, and antisense drugs targeted against XT-I or XT-II to inhibit GAG chain biosynthesis to suppress glial scar formation and promote neuronal regeneration.

Absent evidence to the contrary, an artisan would have expected success, because use of antisense oligonucleotides are well known in the art to inhibit expression of genes by inhibiting mRNA. From the teachings of Kleesiek , it seems possible to use

the knowledge of the cDNA of XT-I and XT-II to make gene therapeutic inhibitors of XT-I and XT-II activity. Finally, Jen et al. suggest that any DNAzyme can be made, using knowledge of a given cDNA. Together, the prior art seems to provide all the known element required for using DNA enzymes for the inhibition of XT-I or XT-II.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (cDNA sequence of XT-I and XT-II; theory of DNAzyme design; importance of XT in glial scar formation and neuroregeneration) are taught by Fawcett or Kleesiek or Jen. It would be therefore predictably obvious to use a combination of these three elements in a method using DNA enzymes (and other inhibitors of mRNA) to XT-I or XT-II to inhibit glial scar formation and promote neural regeneration. Furthermore, the specific DNA enzymes of SEQ ID NO:33 and 39 would be likewise obvious.

Therefore the method as taught by Fawcett et al. in view of Kleesiek and further in view of Jen et al. would have been *prima facie* obvious over the method of the instant application.

Written Description (35 USC 112, first paragraph)

The rejection of claim 28 under 35 USC 112, 1st paragraph (written description) is withdrawn in response to the applicant's claim amendments.

The applicant's claim amendments have been fully considered and are persuasive. The applicant has amended the claims so to recite proteoglycan enzymes that digest a genus of known proteoglycan sugars. The examiner accepts that one of skill in the art would know what these enzymes are.

Therefore, the examiner hereby withdraws the rejection of claim 28 under 35 USC 112, 1st paragraph (written description).

NEW GROUNDS - CLAIM OBJECTION

Claim Objections

Claim 28 is objected to because of the following informalities: The instant claim contains the misspelled word, "protoglycan." Additionally, the examiner recommends changing "protoglycan" to "a proteoglycans." Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fawcett et al. (Brain Research Bulletin. 1999; 49(6): 377-391) in view of Kleesiek (WO01/49831) and further in view of Jen et al. (Stem Cells 2000; 18:307-319).

The teachings of Fawcett et al. in view of Kleesiek and further in view of Jen et al. are described above in the previous 35 USC § 103 section.

Claim 28 has been amended to recite: the method of claim 26, further comprising administering an enzyme that digests a proteoglycan sugar wherein the enzyme digests

a proteoglycans sugar selected from the group consisting of neurocan, NG2, phosphacan.

Fawcett suggests using enzymes which digest proteoglycans to thereby inhibit glial scar formation. Fawcett teaches that there are at least 4 different means to promote axon regeneration: (a) remove cells that produce molecules that inhibit axon regeneration, (b) reduce synthesis of molecules that inhibit axon regeneration, (c) block the activity of molecules that inhibit axon regeneration, and (d) degrade molecules that inhibit axon regeneration (page 384, col.1, last parag.). Furthermore, Fawcett teaches that glycosaminoglycans are molecules which inhibit neuronal growth. Furthermore, Fawcett teach that neurocan, NG2, and phosphacan are proteoglycans that are upregulated during CNS injury and increased in areas of gliosis and that axon regrowth stops exactly where these proteoglycans are deposited (page 382, col.1, lines 11-15). Accordingly, Fawcett suggest inhibiting glial scar formation by using enzymes which digest GAGs and specifically neurocan, NG2, and phosphacan.

In addition, Fawcett suggests using neurotrophic factors to promote neural regeneration. Fawcett suggests using trophic factors for promoting axonal regeneration (page 381, col.2, lines2-4). Additionally, the Conclusion of Fawcett suggests controlling recruitment of different cell types using trophic factors. Furthermore, Fawcett contains the phrase, "exposure to neurotrophins blocks inhibition of axonal regeneration" (page 387, col.1). In the context of Fawcett, a skilled artisan would view treatment of glial scars with "trophic factors" as suggesting neurotrophic trophic factors. While Fawcett indicates that several different growth factors can be used to help

regenerate neurons, none of the cited art specifically recites using nerve growth factor (NGF). However, as the scope of the method is involved in regenerating neurons, the examiner asserts a skilled artisan would use neurotrophic factors, such as nerve growth factor in a method of inhibiting glial scars and promoting neuronal regeneration because NGF induces the differentiation and survival of neurons and is critical for the survival and maintenance of sympathetic and sensory neurons.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to reduce GAG content in a glial scar and promote neuronal regeneration in a subject by inhibiting XT-I or XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs. Furthermore, it would be obvious to co-administer neurotrophic factors and enzymes which digest proteoglycans.

The person of ordinary skill in the art would have been motivated to combine the teachings of Fawcett et al., Kleesiek, and Jen et al. in a method using (1) DNA enzymes (and other inhibitors of mRNA) to XT-I or XT-II, (2) neurotrophic factors, and (3) enzymes which digest proteoglycans to inhibit glial scar formation and promote neural regeneration. Fawcett et al. suggest that inhibiting synthesis of GAG would promote neuronal regeneration, while Kleesiek et al. suggest inhibiting XT using knowledge of the XT cDNA sequence and Jen et al. suggest ribozyme, DNAzyme and antisense design for any DNA sequence. In addition, Fawcett suggests using enzymes which digest proteoglycans to thereby inhibit glial scar formation. In addition, Fawcett suggests using neurotrophic factors to promote neural regeneration.

The scientific logic for practicing the instant invention is this: (1) The cited art (Fawcett) teaches that axons in damaged CNS do not regenerate because of the inhibitory nature of glial scars and that preventing GAG chain synthesis suppresses scar formation, (2) Fawcett suggests targeting GAG synthesis and provides a variety of methods, but does not recite using antisense nucleic acids (3) Kleesiek discovered the genes for xylosyltransferase-I (XT-I) and xylosyltransferase-II (XT-II) which are required for GAG biosynthesis and further teach generic inhibitors of XT-I and XT-II, and (4) Jan et al. teach that any known gene can be inhibited using RNAi, DNAzymes, Ribozymes, and antisense drugs; therefore, a skilled artisan would deem it scientifically logical to use RNAi, DNAzymes, Ribozymes, and antisense drugs targeted against XT-I or XT-II to inhibit GAG chain biosynthesis to suppress glial scar formation. Furthermore, it would be obvious to co-administer neurotrophic factors and enzymes which digest proteoglycans, because neurotrophic factors promote neuronal regeneration and enzymes which digest proteoglycans can provide agents which act against GAG formation by a different mechanism. MPEP 2144.06 indicates that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Absent evidence to the contrary, an artisan would have expected success, because use of antisense oligonucleotides are well known in the art to inhibit expression

of genes by inhibiting mRNA. From the teachings of Kleesiek , it seems possible to use the "knowledge of the cDNA of XT-I and XT-II to make gene therapeutic inhibitors of XT-I and XT-II activity. Finally, Jen et al. suggest that any DNAzyme can be made, using knowledge of a given cDNA. Together, the prior art seems to provide all the known element required for using DNA enzymes for the inhibition of XT-I or XT-II.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (cDNA sequence of XT-I and XT-II; theory of DNAzyme design; importance of XT in glial scar formation and neuroregeneration) are taught by Fawcett or Kleesiek or Jen. It would be therefore predictably obvious to use a combination of these three elements in a method using DNA enzymes (and other inhibitors of mRNA) to XT-I or XT-II to inhibit glial scar formation and promote neural regeneration. Furthermore, the specific DNA enzymes of SEQ ID NO:33 and 39 would be likewise obvious. The cited art also suggest the elements of: co-administering (1) neurotrophic factors and (2) enzymes which digest proteoglycans

Therefore the method as taught by Fawcett et al. in view of Kleesiek and further in view of Jen et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633